Dependence of Castration-Resistant Prostate Cancer (CRPC) Stem Cells on CRPC-Associated Fibroblasts.

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Public Summary:

More than 20,000 American men die every year from prostate cancer. Most of them die because their cancer fails androgen ablation therapy, a.k.a. chemical castration. It is well known that prostate cancer progression depends not only on prostate epithelial cells per se, but also on supporting (stromal) cells present in the gland and known as cancer-associated fibroblasts (CAFs). One important role of these CAFs is to support prostate cancer stem cells, which have the capacity to grow Indefinitely. This knowledge, however, comes from studies of early, androgen-dependent disease models. The role of stromal cells in lethal, castration-resistant prostate cancer, is not well defined. In the present study, Adisetiyo et al. used a mouse model of castration-resistant prostate cancer, the lethal disease for which there is no cure. They showed that CAFs continue to support cancer stem cells present in the castration-resistant tumors. Remarkably, however, these CAFs are quite different from CAFs present in early, androgen-dependent tumors. CAFs found in castration resistant tumors support growth of cancer stem cells from the same tumors much better than CAFs, even much larger number of CAFs, from early, androgen-dependent tumors. Thus, in order to ultimately save the lives of prostate cancer that fails androgen ablation therapy, future investigation of the interaction between CAFs and prostate cancer stem cells must take into consideration changes that the CAFs undergo as tumors become castration-resistant.

Scientific Abstract:

We previously established a role for cancer-associated fibroblasts (CAFs) in enhancing the self-renewal and differentiation potentials of putative prostate cancer stem cells (CSCs). Our published work focused on androgen-dependent prostate cancer (ADPC) using the conditional Pten deletion mouse model. Employing the same model, we now describe the interaction of CAF and CSC in castration-resistant prostate cancer (CRPC). CAF isolated from ADPC (ADPCAF) and from CRPC (CRPCAF) were compared in terms of their ability to support organoid formation and tumor initiation by CSC from CRPC (CRPCSC) in vitro and in vivo. CRPCSC formed spheroids in vitro and well-differentiated glandular structures under the renal capsules of recipient mice in vivo more effectively in the presence of CRPCAF compared to ADPCAF. Furthermore, whereas CSC with CAF from ADPC formed mostly well-differentiated tumors in our previous study, we now show that CRPCSC, when combined with CRPCAF (but not ADPCAF) can form aggressive, poorly differentiated tumors. The potential of CRPCAF to support organoid/tumor formation by CRPCSC remained greater even when compared to 10-fold more ADPCAF, suggesting that paracrine factors produced specifically by CRPCAF preferentially potentiate the stemness and tumorigenic properties of the corresponding CSC. This apparently unique property of CRPCAF was notable when the CAF and CSC were grafted in either intact or castrated recipient mice. In both environments, CRPCAF induced in the epithelial compartment higher proliferative activity compared to ADPCAF, indicated by a higher Ki67 index. Factors released by CRPCAF to regulate CRPCSC may be targeted to develop novel therapeutic approaches to manage prostate cancer. J. Cell. Physiol. (c) 2014 Wiley Periodicals, Inc.